(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) EP 0 908 181 A1

(12) EUROPEAN PATENT APPLICATION

published in accordance with Art. 158(3) EPC

(43) Date of publication:
14.04.1999 Bulletin 1999/15

(21) Application number: **97922088.6**

(22) Date of filing: **19.05.1997**

(51) Int. Cl.[6]: **A61K 31/435**, C07D 455/04

(86) International application number:
PCT/JP97/01667

(87) International publication number:
WO 97/44034 (27.11.1997 Gazette 1997/51)

(84) Designated Contracting States:
DE ES FR GB IT

(30) Priority: **20.05.1996 JP 124531/96**

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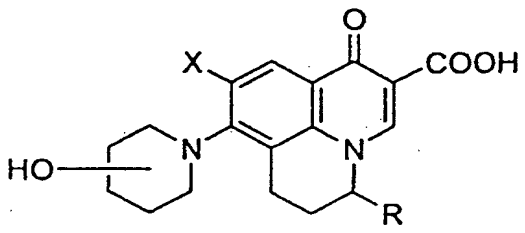
(54) REMEDY FOR ROSACEA

(57) A rosacea treating agent is provided, which is effective even on intractable rosacea which cannot be cured completely by antibiotics such as minocycline, has low toxicity, causes little side effect, and is of long duration. The rosacea treating agent of the present invention comprises, as an active ingredient, at least one selected from the group consisting of benzoheterocyclic derivatives represented by the following formula (1):



(1)

wherein R is a lower alkyl group; and X is a halogen atom, and salts thereof.

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on which conventional antibiotics such as minocycline do not work, healing rosacea active papules, active pustules, erythema, and active efflorescence, and suppressing telangiectasia. It has low toxicity, causing little side effect, and is of long duration.

Best Embodiments for Carrying Out the Invention

[0012] The rosacea treating agent according to the present invention comprises at least one selected from the group consisting of the above benzoheterocydic derivatives represented by formula (1) and salts thereof as an active ingredient.

[0013] In formula (1), the lower alkyl group represented by R includes straight-chain or branched alkyl groups having 1 to 6 carbon atoms, such as methyl, ethyl, propyl, isopropyl, butyl, *tert*-butyl, pentyl and hexyl groups. The halogen atom represented by X includes a fluorine atom, a chlorine atom, a bromine atom, and an iodine atom.

[0014] Of the compounds represented by formula (1), (±)-9-fluoro-6,7-dihydro-8-(4-hydroxy-1-piperidyl)-5-methyl-1-oxo-1H,5H-benzo[i,j]-quinolizine-2-carboxylic acid is particularly preferred.

[0015] The compound represented by formula (1) can be easily converted into acid-addition salts thereof by the reaction with a pharmaceutically acceptable acid. The acid includes inorganic acids, such as hydrochloric acid, sulfuric acid, phosphoric acid, and hydrobromic acid; and organic acids, such as oxalic acid, maleic acid, fumaric acid, malic acid, tartaric acid, citric acid, and benzoic acid. The compounds represented by formula (1) can easily be converted into salts thereof by the reaction with a pharmaceutically acceptable alkaline compound. The alkaline compound includes sodium hydroxide, calcium hydroxide, potassium hydroxide, sodium carbonate, and potassium hydrogencarbonate.

[0016] The compound represented by formula (1) of the present invention and salts thereof can be easily isolated and purified by ordinary separation means, such as solvent extraction, dilution, recrystallization, column chromatography, preparative thin layer chromatography, and the like.

[0017] In using the compound represented by formula (1) and salts thereof as a rosacea treating agent, they are generally compounded into pharmaceutical compositions together with pharmaceutically acceptable carriers which are commonly employed in preparing drugs of dose form conformable to the method of administration. Suitable carriers which can be used include diluents or excipients, such as fillers, extenders, binders, wetting agents, disintegrants, surfactants, lubricants, etc.

[0018] The rosacea treating agent can have various dosage forms in accordance with the purpose of the therapy. Typical dosage forms include tablets, pills, powders, livid preparations, suspensions, emulsions, granules, capsules, suppositories, injectable preparations (solutions, suspensions, etc.); sprays, such as inhalations and aerosol for external use; liquids for topical application, lotions, gels, oily ointments; emulsified ointments, such as O/W hydrophilic ointments and W/O water-absorbent ointments; water-soluble ointments, creams, liniments, cataplasms, pastes, plasters, external preparation such as emulsions, and sheets.

[0019] If the pharmaceutical composition is formulated into tablets, a wide range of carriers known in the art can be used. Examples of suitable carriers include excipients such as lactose, white sugar, sodium chloride, glucose, urea, starch, calcium carbonate, kaolin, crystalline cellulose, and silicic acid; binders such as water, ethanol, propanol, simple syrup, a glucose solution, a starch solution, a gelatin solution, carboxymethyl cellulose, shellac, methyl cellulose, potassium phosphate, and polyvinylpyrrolidone; disintegrants such as dried starch, sodium alginate, agar powder, laminaria powder, sodium hydrogencarbonate, calcium carbonate, polyoxyethylene sorbitan fatty acid esters, sodium laurylsulfate, glycerol monostearate, starch, and lactose; disintegration inhibitors such as white sugar, stearin, cacao butter, and hydrogenated oils; absorption promoters such as quaternary ammonium bases and sodium laurylsulfate; humectants such as glycerol and starch; adsorbents such as starch, lactose, kaolin, bentonite, and colloidal silicic acid; and lubricants such as purified talc, stearic acid salts, boric acid powder, and polyethylene glycol. The tablets, if desired, can be coated tablets having a general coat, such as sugar-coated tablets, gelatin-coated tablets, enteric coated tablets, film-coated tablets, double-layered coated tablets, or multilayered coated tablets. In formulating into pills, carriers well known in the art can be used widely. Examples of suitable carriers are excipients such as glucose, lactose, starch, cacao butter, hardened vegetable oils, kaolin, and talc; binders such as gum arabic powder, tragacanth powder, gelatin, and ethanol; and disintegrants such as laminaria and agar. In formulating into suppositories, carriers well known in the art can be used widely. Examples are polyethylene glycol, cacao butter, higher alcohols, higher alcohol esters, gelatin, and semisynthetic glycerides. Capsules are generally prepared by mixing the active ingredient with the above-enumerated various carriers and packing the mixture into hard gelatin capsules or soft capsules. Solutions, emulsions or suspensions as injectable preparations are preferably sterilized and made isotonic with blood. In preparing these preparations, all diluents customarily used in the art, such as water, ethanol, Macrogol, propylene glycol, ethoxylated isostearyl alcohol, polyoxylated isostearyl alcohol, and polyoxyethylene sorbitan fatty acid esters, can be used. Sodium chloride, glucose or glycerol may be incorporated into the injectable preparation in an amount sufficient for making it isotonic. The injectable preparations can contain general dissolution aid, buffers, pain-alleviating agents, and the like. The pharmaceutical compositions can contain coloring agents, preservatives, perfumes, flavors, sweeteners, and other

(continued)

Total	5 ml

[0027] The compound of formula (1) and glucose were dissolved in injectable distilled water, and the solution was put into a 5 ml-volume ampule. After substitution with nitrogen, the solution was sterilized by autoclaving at 121°C for 15 minutes to obtain an injection having the above composition.

Formulation Example 2

[0028]

Compound of formula (1)	100 g
Avicel (trade name, a product of Asahi Chemical Industry Co., Ltd.)	40 g
Corn starch	30 g
Magnesium stearate	2 g
Hydroxypropylmethyl cellulose	10 g
Polyethylene glycol-6000	3 g
Castor oil	40 g
Ethanol	40 g

[0029] The compound of the invention, Avicel, corn starch, and magnesium stearate were mixed, ground, and punched using a pestle of sugar coating R=10 mm. The resulting tablets were coated with a film coating agent comprising hydroxypropyl methyl cellulose, polyethylene glycol-6000, castor oil and ethanol to obtain film-coated tablets.

Formulation Example 3

[0030]

(±)-9-Fluoro-6,7-dihydro-8-(4-hydroxy-1-piperidyl)-5-methyl-1-oxo-1H,5H-benzo[i,j]quinolizine-2-carboxylic acid	2 g
Purified lanolin	5 g
White beeswax	5 g
White petrolatum	88 g
Total	100 g

[0031] White beeswax was liquefied by heating, and the compound of the invention, purified lanolin and white petrolatum were added thereto. After once heated to liquefy, the mixture was stirred till it began to solidify to obtain an ointment of the above composition.

Formulation Example 6

[0035]

Ointment:	
White petrolatum	73.54 g
Light liquid paraffin	10.0 g
Cetanol	5.0 g
Cholesterol	4.0 g
(±)-9-Fluoro-6,7-dihydro-8-(4-hydroxy-1-piperidyl)-5-methyl-1-oxo-1H,5H-benzo[i,j]quinolizine-2-carboxylic acid	1.0 g
Sodium hydroxide	0.112 g
Propylene glycol	5.0 g
Di(β-hydroxyethyl)amine	0.2 g
Disodium edetate	0.1 g
Purified water	1.048 g

Formulation Example 7

[0036]

Component I:	
White petrolatum	6.5 g
Light liquid paraffin	6.0 g
Stearyl alcohol	2.5 g
Cetanol	2.5 g
Polyoxyethylene cetyl ether	2.0 g

Component II:	
(±)-9-Fluoro-6,7-dihydro-8-(4-hydroxy-1-piperidyl)-5-methyl-1-oxo-1H,5H-benzo[i,j]quinolizine-2-carboxylic acid	1.0 g
Sodium hydroxide	0.112 g
Di(β-hydroxyethyl)amine	0.36 g
Purified water	79.028 g

[0037] Component I was heated to about 80°C to melt. Separately, component II was mixed, dissolved, and heated to about 80°C. The heated components I and II were mixed and cooled to obtain an external preparation in emulsion form.

wherein R represents a lower alkyl group; and X represents a halogen atom,
and salts thereof.

2. The rosacea treating agent according to claim 1, wherein the active ingredient is at least one selected from the group consisting of (±)-9-fluoro-6,7-dihydro-8-(4-hydroxy-1-piperidyl)-5-methyl-1-oxo-1H,5H-benzo[i,j]-quinolizine-2-carboxylic acid and salts thereof.

3. Use of at least one compound selected from the group consisting of benzoheterocyclic derivatives represented by formula (1) according to claim 1 and salts thereof for preparing a rosacea treating agent.

4. A method for treating rosacea comprising using at least one selected from the group consisting of benzoheterocyclic derivatives represented by formula (1) according to claim 1 and salts thereof.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP97/01667

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 4
because they relate to subject matter not required to be searched by this Authority, namely:
It pertains to methods for treatment of the human or animal body by therapy.

2. [ ] Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest
[ ] The additional search fees were accompanied by the applicant's protest.
[ ] No protest accompanied the payment of additional search fees.

Form PCT/ISA/210 (continuation of first sheet (1)) (July 1992)